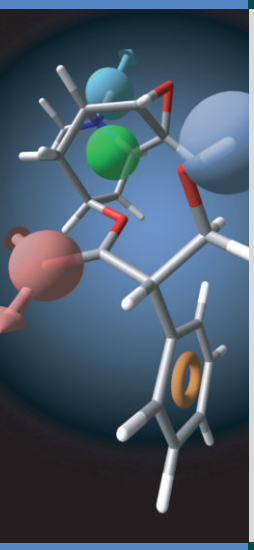


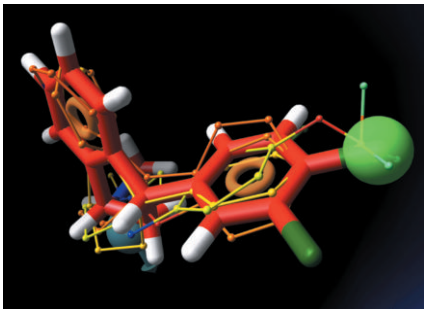
Phase

A high-performance program for ligand-based drug design

Phase is a complete package of pharmacophore modeling tools that offers scientists an unparalleled level of control at each step. Fast, accurate, and highly configurable, Phase is a powerful tool for hit generation and lead hopping.

SCHRÖDINGER.

The Advantages of Pharmacophore Modeling

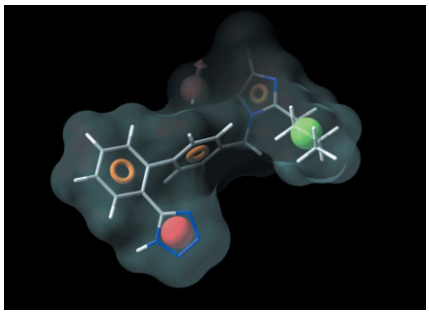


Selective serotonin reuptake inhibitors (SSRIs) are colored according to the quality of their alignment to the Phase hypothesis. Potent ligands align well to the pharmacophore, which is in good agreement with published results.

As researchers continue to search for new targets of therapeutic interest, transmembrane and G-protein coupled receptors are of ever-increasing importance. However, crystal structures for these targets may be impossible to resolve, posing great challenges in rational drug design. Structure-based virtual screening is not an option when the active site geometry is unknown, but assaying an entire library for hits is an inefficient and expensive proposition.

Pharmacophore modeling solves this problem by determining the spatial arrangement of chemical features that confer drug activity toward a target receptor. Having established the chemical space occupied by active ligands, pharmacophore modeling software allows researchers to create 3-D structure-activity relationships, screen databases, and generate hits without the benefit of a receptor structure.

Phase: Maximizing Returns in Lead Discovery

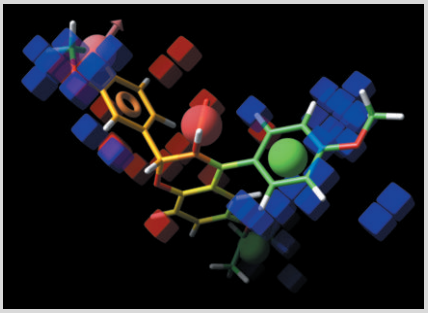


The volume of this pharmacophore hypothesis for angiotensin AT_1 antagonists is represented by a translucent molecular surface. The 6-site pharmacophore is quickly located using Phase's high-dimensional partitioning algorithm.

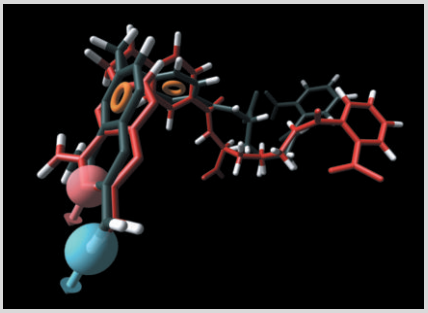
Schrödinger's Phase is a pharmacophore modeling and database screening program specifically designed to bring speed, efficiency, and accuracy to lead discovery efforts. Its features include:

- **Expert levels of control:** Phase distinguishes itself from "black box" software by allowing users to exercise precise control over job settings at all steps, including pharmacophore scoring, QSAR building, and database screening.
- **Universal applicability:** While Phase is well suited to drug discovery projects for which no receptor structure is available, it also allows pharmacophores to be constructed with the aid of a crystal structure.
- **Custom feature definitions:** Phase locates features using SMARTS pattern matching, making it easy to modify existing feature definitions and to create entirely new custom features. Intuitive visualization tools and the rapid location of sites help researchers fine-tune feature definitions.
- **Excluded volumes:** Once a pharmacophore model has been developed, researchers may define regions of space that are presumed to be occupied by the receptor, and therefore off-limits to any ligand.
- **Versatile Database Management:** Phase allows researchers to create and save multi-conformer databases for later screening, or to efficiently generate conformations while searching for hits. Researchers can also retrieve hits from a fully prepared database of commercially available, druglike compounds that is distributed with the software.
- **Easy-to-use interface:** Phase includes an intuitive step-by-step interface that guides researchers through pharmacophore creation, database setup, and database screening.
- **Cross-platform support:** Phase supports Linux and SGI, and features distributed processing for all computationally intense job types to expedite large calculations.

Performance-Driven Technology



The hydrophobic contributions to a Phase QSAR for endothelin-A selective antagonists are represented here by blue and red cubes, while carbon atoms are colored by proximity to various pharmacophore features. The quality of the Phase hypothesis is confirmed by its ability to match a diverse set of known actives.



The bound conformation of PT523, a potent anti-cancer drug, is shown as it appears in a crystal structure (red atoms), and as predicted by the top-scoring Phase hypothesis (gray atoms). The Phase prediction has an RMSD of just 0.78 Å compared to the crystal structure.

Phase equips researchers with novel, highly efficient technology for pharmacophore modeling:

- **Thorough conformation generation:** Phase uses Schrödinger's ConfGen technology to perform systematic explorations about rotatable bonds and calculate associated conformational energies, retaining only the most reasonable conformations.
- **Rapid pharmacophore identification:** Phase quickly locates plausible pharmacophores using a proprietary high-dimensional partitioning algorithm in which pharmacophores from different conformations are placed in multi-dimensional boxes. Each box represents a common pharmacophore only if it contains a sufficient number of active ligands.
- **Advanced pharmacophore scoring:** After Phase has located reasonable alignments of active ligands, pharmacophores are evaluated according to an open, highly configurable scoring function. Researchers can impose cutoffs to reject unwanted pharmacophores, and enable, disable, and weigh scoring terms as they see fit.
- **3-D QSAR:** Phase determines how molecular structure affects drug activity by dividing space into a fine cubic grid, encoding atom type occupation as numerical information, and performing a partial least-squares (PLS) regression.
- **Rapid database screening:** Phase employs 2-D and 3-D database keys to efficiently eliminate molecules that cannot provide hits. Researchers may request partial or full matches to a pharmacophore model, emphasize various aspects of matching through an adjustable fitness measure, apply an excluded volume filter, and predict activity using a QSAR hypothesis.

Accurate pharmacophore models

A pharmacophore is useful only if it accurately represents the arrangement of chemical features that drive ligand binding. By comparing pharmacophores predicted by modeling software to those derived from crystal structures, it is possible to gauge a program's ability to reproduce ligand binding modes. In this regard, Phase demonstrates outstanding performance.

In a head-to-head comparison across a previously published test set of five pharmaceutical targets, Phase generated high-ranking hypotheses that aligned very well with pharmacophores derived from crystal structures. These results were uniformly comparable or superior to those produced by Catalyst. For most targets, Phase returned a better alignment to the crystal structures, while Catalyst offered significantly worse performance for HIV-RT and CDK-2.

	Best Phase Hypothesis	
Target	RMSD	Rank
DHFR	0.78 Å	1
Thrombin	2.45 Å	3
Thermolysin	1.40 Å	9
HIV-RT	0.10 Å	3
CDK-2	0.34 Å	4

	Best Catalyst Hypothesis	
Target	RMSD	Rank
DHFR	1.06 Å	2
Thrombin	2.27 Å**	2
Thermolysin	1.96 Å	8
HIV-RT	0.07 Å	18
CDK-2	1.40 Å	2

** Catalyst failed to return all pharmacophore features identified in crystal structure

Evaluation Copies

To request an evaluation copy of Phase, please contact info@schrodinger.com. Our staff of support scientists will be happy to assist you in giving Phase a thorough trial.

Phase

A high-performance program for ligand-based drug design

System Requirements:

LINUX
- Pentium or better
- Linux kernel 2.4 (Red Hat 7.3) or later
- 256 MB memory

SGI
- R5000 or better
- IRIX 6.5.2m or later
- 256 MB memory

Additional Information:

www.schrodinger.com
info@schrodinger.com

A Coordinated Family of Products

Phase is a powerful tool for ligand-based drug design, and can also be used as an adjunct to structure-based drug-discovery projects. Schrödinger's FirstDiscovery Suite is an ideal complement to Phase. The FirstDiscovery Suite consists of three integrated modules for structure-based drug design:

- **Glide:** High-throughput ligand-receptor docking for fast library screening
- **Liaison:** Ligand-receptor binding free energies for lead optimization
- **QSite:** Mixed QM/MM for reactive chemistry at the enzyme active site

All Schrödinger products are seamlessly integrated through the Maestro graphical interface.

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